PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.11.2004
Applicant's or agent's file reference: P1312 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/29062	16.09.2003	22.10.2002

Applicant: MEDTRONIC AVE, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1312 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/29062	International filing date *(day/month/year)* 16.09.2003	Priority date *(day/month/year)* 22.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K48/00		
Applicant MEDTRONIC AVE, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.05.2004	29.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Böhmerova, E Telephone No. +49 89 2399-7859

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/29062

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-21 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-19

   because:

   ☒ the said international application, or the said claims Nos. 1-19 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12-14
	No:	Claims	1-11,15-28
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	20-28
	No:	Claims	-

2. Citations and explanations

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/29062

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

D1: WO 97/16169 A (CHIRON CORP) 9 May 1997

D2: SHARIFI BEHROOZ G ET AL: "Adeno-associated virus-mediated apo A-I milano genetherapy for atherosclerosis and restenosis" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001, pages 270A-271A

D3: CHEN M ET AL: "DEVELOPMENT AND CHARACTERIZATION OF A RECOMBINANT TRUNCATED TYPE VII COLLAGEN MINIGENE" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, vol. 275, no. 32, 11 August 2000, pages 24429-24435

D4: SHAH PREDIMAN K ET AL: "High-dose recombinant apolipoprotein A-Imilano mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein E-deficient mice: Potential implications for acute plaque stabilization" CIRCULATION, vol. 103, no. 25, 26 June 2001, pages 3047-3050

D5: CHIESA GIULIA ET AL: "Recombinant apolipoprotein A-IMilano infusion into rabbit carotid artery rapidly removes lipid from fatty streaks" CIRCULATION RESEARCH, vol. 90, no. 9, 17 May 2002, pages 974-980

D6: BARNES MICHAEL J ET AL: "Collagens and atherosclerosis" EXPERIMENTAL GERONTOLOGY, vol. 34, no. 4, July 1999, pages 513-525

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty

The subject-matter of claims 1-11, 15-19 lacks novelty under Art. 33(1) and (2) PCT over the disclosure of D1 teaching the use of gene therapy in the treatment and prevention of cardiovascular diseases including plaque rupture. The subject-matter of claims 20,21,23-26,28 lacks novelty over D2 disclosing adeno-associated virus coding apo A-I Milano and the use thereof for the treatment of atherosclerosis. The subject-matter of claims 20-22, 25,26,28 lacks novelty under over the disclosure of D3 teaching eucaryotic expression vector coding truncated collagen VII gene.

The subject-matter of claims 12-14 is considered to be novel under Art. 33(1) and (2) PCT as none of the cited documents teaches the use of a nucleic acid coding for a collagen isoform or apolipoprotein A1 isoform in the treatment of vulnerable plaque.

Inventiveness

As the subject-matter of claims 1-11, 15-28 is considered as lacking novelty, no inventiveness can be acknowledged in this stage.

The subject-matter of claims 13,14 is considered as lacking an inventive step under Art. 33(1) and (3) PCT for the following reasons: The beneficial effect of Apo A1 Milano on vulnerable plaque stabilisation is known from D4 and D5. Taking into the account this known activity, it would be obvious to a person skilled in the art to employ nucleic acid coding for Apo A1 in the method of gene therapy for preventing plaque rupture as known from D1. Furthermore, the application does not prove that the claimed solution actually solves the technical problem as there are no experimental data showing any effect of the gene therapy as claimed on the vulnerable plaque.

The subject-matter of claim 12 is considered as lacking an inventive step under Art. 33(1) and (3) PCT for the following reasons: It is known from D6 that collagen type I plays the pivotal role in plaque stability and that an important factor leading to plaque instability is proteolysis of collagen(s) in the cap by metalloproteinases. Taking into the consideration this disclosure of D5, it would be obvious to a person skilled in the art to use a collagen isoform gene in the method known form D1. Furthermore, analogically as in the case of Apo A1 Milano gene above, there is no prove in the application that

the solution claimed in claim 12 actually solves the technical problem.

Industrial applicability

Subject-matter of independent claims 20-28 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 1-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.